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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/544,910	04/07/2000	Yadong Huang	06510/121US1	2429

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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/544,910	HUANG ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-8 and 11-35* is/are pending in the application.

4a) Of the above claim(s) *12-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-8, 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on November 22, 2006.

Currently, claims 1, 4-8, 11-35 are pending. Applicants have cancelled claims 2-3 and 9-10. Claims 12-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 112, first paragraph

Claims 1, 4-8, and 11 remain rejected under 35 U.S.C. 112, first paragraph, as failed to comply with the enablement requirement for the reasons of record as set forth in the Office action mailed on May 23, 2006 and for the reasons stated below.

Applicant's arguments filed on November 22, 2006 have been fully considered but they are not persuasive.

The claims are directed to a method for reducing the plasma level of VLDL in a host comprising administering an antisense nucleic acid targeted to ApoE3, wherein the host suffers from hyperlipidemia.

As applicants acquiesced in the remarks filed on November 22, 2006, the instantly claimed invention reads only on an *in vivo* method. Applicants are correct that the state of the art of making and using nucleic acids to modulate gene expression, given the nucleotide sequence of a given gene, was such that one skilled in the art could readily design, make, and use antisense nucleic acids that would reduce the expression of the gene, at the time of filing (page 7). Nonetheless, this facile design and use of antisense nucleic acids are applicable only to a method drawn to *in vitro* gene inhibition performed on a benchtop or in a cell culture room. As applicants have asserted, the antisense technology at the time of filing was relatively well-developed; however, *in vivo,* therapeutic applications of the antisense technology were far from being well-established. That is, one skilled in the art could not have readily extrapolated any *in vitro* data obtained from the benchtop experimental science to predict the requisite *in vivo* pharmaceutical/therapeutic effects in a living organism/host. Applicants assert that the only experiments needed to meet the enablement requirements in the instant case are those designed to determine which antisense nucleic acids retain the ability to reduce expression of ApoE, which employ techniques and experiments that are routine in the art (page 9). Again, this assertion is only applicable to *in vitro* methods of administering an antisense nucleic acid into cultured cells. Persons of ordinary skill in the art would reach a unanimous consensus on the fact that *in vivo*

clinical testing of any antisense nucleic acid is not considered routine in the art because clinical trials, especially treatment trials for new therapeutics, entail extensive, comprehensive, and thorough steps of evaluating the desired therapeutic effects in various groups of participating human subjects. In fact, the state of the "gene therapy" art was far from being both well-understood and widely practiced at the time of filing. In 1999, according to an article published by the Oak Ridge National Laboratory for the Department of Energy, gene therapy suffered a major setback with the death of 18-year-old Jesse Gelsinger, who participated in a gene therapy trial for ornithine transcarboxylase deficiency. It was determined that he died from multiple organ failures four days after starting the treatment. See page 1 of 1. Further, the article clearly teaches what requirements are need to be met and what factors must be considered before determining therapeutic efficacy of any gene therapeutic agent. The factors include 1) that the therapeutic DNA introduced into target cells must remain functional and the cells containing the therapeutic DNA must be long-lived and stable; 2) that the therapeutic DNA introduced into an organism does not trigger the immune system; 3) that the carriers of the therapeutic DNA introduce problems related to toxicity, immune and inflammatory responses; and 4) that many disorders including diabetes are caused by the combined effects of variations in many genes and the multi-factorial disorders would be difficult to treat effectively using gene therapy.

If any antisense nucleic acid inhibitors were designed in a laboratory and readily used in clinical applications without undergoing proper stages of clinical or *in vivo* tests, that is without "undue experimentation", as applicants contend in their Remarks, one might reasonably ask why there is only one antisense-based therapeutic agent (Vitravene) approved by the FDA to date since the discovery of antisense nucleic acids in 1978 by Zamecnik and Stephenson (*PNAS,*

1978, 75:280-284). See the reference citation. As such, it is an art-recognized viewpoint that having an antisense sequence in hands does not indeed mirror therapeutic efficacy of the antisense sequence and that one skilled in the art cannot determine the therapeutic efficacy of the antisense nucleic acid without undue experimentation. This art-recognized knowledge pertinent to the difficulties and unpredictable *in vivo* pharmacokinetics of antisense nucleic acids was not refuted by the end of the year 2003. See for example the review article by Scherer et al. (*Nature Biotechnology,* 2003, 21:1457-1465). The reference explicitly teaches that the *in vitro* inhibition data of an antisense nucleic acid are not correlative with the *in vivo* therapeutic effects of the antisense agent. See the passages on page 1457 cited below:

"Over the past 25 years there have been thousands of published reports describing applications of antisense nucleic acid derivatives for targeted inhibition of gene function....Whatever the method, the problems for effective application are remarkably similar: efficient delivery, enhanced stability, minimization of off-target effects and identification of sensitive sites in the target RNAs. These challenges have been in existence from the first attempts to use antisense research tools, and need to be met before any antisense molecule can become widely accepted as a therapeutic agent".

"In subsequent years, however, interest declined because the predicted utility of these compounds (refereeing to antisense oligonucleotides) as therapeutic agents was slow to materialize and, in fact, remains limited to a handful of compounds".

In order to overcome the art-recognized unpredictability of nucleic acid drugs (i.e., antisense nucleic acids, also see references by Mercola et al. and Branch as cited in the previous Office action), the specification must provide sufficient guidelines so as to produce the claimed

therapeutic effects when the instantly claimed methods are practiced by one of ordinary skill in the art. As previously stated in the Office action mailed to the applicants on May 23, 2006, the instant specification is devoted to disclosing a correlative relationship between the overexpression of ApoE3 and the increased levels of VLDL found in hyperlipidemic subjects. See pages 4-5 of the previous Office action. The specification is completely silent about the structure, the function, or combination thereof with regard to the instantly claimed antisense nucleic acid that can treat a hyperlipidemic host. In fact, the entire disclosure of the instant application is silent about *in vitro* inhibitory effects pertinent to the ApoE3 antisense nucleic acid, let alone the claimed *in vivo* therapeutic effects exerted by the ApoE3 antisense nucleic acid.

Moreover, the instant disclosure does not set forth any specific guidance/direction as to how to practice the instantly claimed treatment method (i.e, method steps or protocols) or how to obtain the therapeutic effects required by the claims. For instance, one of ordinary skill in the art would not know what is embraced by the term "effective amount" because there are no guidelines for determination of antisense dosages needed to provide a therapeutic effect and there is no standard by which to measure whether the ApoE antisense nucleic acids will therapeutically operate *in vivo* as intended and claimed. The specification merely states that the "effective amount" is a dosage sufficient to produce the desired amount of VLDL and that those of skill in the art will readily appreciate that dose levels can vary such that from about 1ng to 1mg, usually from about 1μg to 100 μg. See page 17. The mere statement that various amounts can be used in a wide range of suggested dosage does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use any ApoE antisense nucleic acid for

therapeutic applications in all organisms *in vivo* as broadly claimed in the instant case, let alone in a patient who suffers from an elevated VLDL levels. Note that the claims, as recited, are directed to the methods of reducing the plasma level of VLDL in a host and treating a host suffering from a disease condition associated with elevated plasma levels of VLDL, not to a method of inhibiting ApoE expression in a host. To reiterate for emphasis, the instant specification only provides the correlation between high level of ApoE and high level of VLDL found in subjects having hyperlipidemia, but it fails to provide any concrete, substantial evidence that inhibiting the ApoE3 expression *in vivo* indeed reduces the VLDL amount to a desired level by administering an ApoE3 antisense nucleic acid in any host. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of treating a subject comprising administering a therapeutically effective amount of an antisense nucleic acid to ApoE3.

In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991), the Court ruled that a rejection under 35 U.S.C. 112, first paragraph for lack of enablement was appropriate given the relatively incomplete understanding in the biotechnological field involved, and the lack of a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims.

Further, the broadly claimed methods without reciting the specific structure of the lectin ligand (i.e., SEQ ID NOs and type of target ApoE) in claims 1 and 5-8 encompass any nucleic acid sequence to any ApoE, which is required to elicit pharmaceutical/therapeutic activity in any living organism toward any ApoE. As such, one of ordinary skill in the art must be able to practice the claimed method of treating or reducing high levels of VLDL in a subject by

administering an undisclosed, unknown antisense nucleic acid agent targeted to any ApoE mRNA sequence. Contrary to applicants' assertions that no serious undue experimentation is necessary to practice the claimed invention, it is deemed that one of skill in the art would not have been able to carry out the steps required to practice the full scope of the claims in light of the breadth of the claims, the nature of the invention, the state of the art, the level of one of ordinary skill, the unpredictability of the art, the amount of direction provided by the inventors, the existence of working examples, and the quantity of experimentation necessary to use the invention based on the content of the disclosure.

Corollary to the instant case, in *In re Wright,* 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993), the court affirmed the Board's decision and stated that the evidence did not show that a skilled artisan would have been able to carry out the steps required to practice the full scope of claims which encompass "any and all live, non-pathogenic vaccines, and process for making such vaccines, which elicit immunoprotective activity in any animal toward any RNA virus." 999 F.2d at 1562, 27 USPQ2d at 1513 (original emphasis).

Accordingly, in view of the totality of the factors and reasons stated above, it would require undue experimentation for one skilled in the art to practice the entire scope of the claimed invention at the time of filing, and therefore a rejection under 35 U.S.C. 112, first paragraph for lack of enablement is appropriate.

Conclusion

No claim is allowed.

This application contains claims 1 and 5 drawn to inventions (a ribozyme and an antisense conjugate) nonelected with traverse in the reply filed on April 20, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

TC1600

JANE ZARA, PH.D.
PRIMARY EXAMINER